

Association Of Elevated Ldh And Hypocalcemia In Dengue Fever And Its Severity And Outcomes

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ABSTRACT:

Dengue fever (DF) and its severe forms - dengue hemorrhagic fever (DHF) and dengue shock syndrome (DSS) have become major public health concerns in our country. There arises a need to study the biochemical markers which can depict prognosis and point towards the deteriorating course of disease early before such complications arise. We investigated 85 patients, who were dengue NS1 or IgM positive. This study aims to identify the utility of LDH and S. ionized calcium as a prognostic marker and outcome predictor in Dengue Fever. We observed a median value of LDH in patients with severe dengue to be 1675.5U/L, followed by 799.5U/L in dengue with warning signs and 388U/L in dengue without warning signs. (p-value < 0.0001). The median value of ionized calcium in severe dengue was observed to be 0.99mmol/L which was significantly lower than in dengue with warning signs (1.12mmol/L) and dengue without warning signs (1.26mmol/L) (p-value <0.0001). Thus, hypocalcemia and higher LDH are dependable markers to prognosticate the course of outcomes in Dengue fever.

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I. BACKGROUND:

Dengue fever (DF) and its severe forms - dengue hemorrhagic fever (DHF) and dengue shock syndrome (DSS) have become major public health concerns in our country. Complicated Dengue (DHF, DSS) carries a high morbidity and mortality burden. Hence, there arises a need to study the biochemical markers which can depict prognosis and point towards the deteriorating course of disease early before such complications arise. Thus, patients with such deranged markers can be aggressively managed and improvement in outcomes can be hoped for to decrease morbidity and mortality burden.[1]

LDH is an intracellular enzyme abundantly found in body tissues and is increased in dengue fever. LDH levels are higher in DHF & DSS patients and an early increase in LDH is an independent predictor of DHF. Significant hypocalcemia occurs in the critical phase of DHF. This study aims to identify the utility of LDH and S. ionized calcium as a prognostic marker and outcome predictor in Dengue Fever.[2]

II. METHODS:

We investigated 85 patients, who were dengue NS1 or IgM positive and who were admitted to the medicine department of SSGH, Vadodara. Since the study interval was of 10 months duration and considering the seasonal peak of dengue fever, we had estimated a sample size of 83 patients and hence enrolled 85 patients for the study. After clinical history & thorough clinical examination patients fulfilling inclusion criteria were enrolled and a prospective observational study was undertaken.

III. METHODOLOGY:

After enrollment the following investigation was sent:

CBC, PSMP, PT/APTT, RFT, LFT, Na⁺, K⁺, S. Ionized calcium, LDH, Total protein, serum albumin, Dengue Ns1/IgM, Widal, X-ray chest, USG abdomen pelvis and ECG. Patients were followed up throughout their period of hospitalization up to their discharge. They were divided into three categories based on their clinical features and investigations: Dengue without a warning sign, dengue with a warning sign, and severe dengue. The results of S. Ionized calcium and LDH were then studied with the severity and outcome in patients with dengue fever.

INCLUSION CRITERIA:

The patient's having dengue NS1/IgM positive and was admitted to the medicine department of SSGH, Vadodara.

EXCLUSION CRITERIA:

- 1) Haemolytic anemia
- 2) Parathyroid disorders
- 3) HTN/DM/CV STROKE
- 4) Renal/ Liver failure
- 5) Dengue with co-infections like malaria or typhoid
- 6) Patients on calcium supplements and tablets like CCB or Bisphosphonates
- 7) Acute pancreatitis
- 8) Patients with crush injuries/muscle/bone trauma

IV. RESULTS:

Table 1:-Distribution of serum LDH(U/L)of study subjects.

Serum LDH(U/L)	Frequency	Percentage
Serum LDH(U/L)		
Normal{230-460}	36	42.35%
Deranged	49	57.65%
Mean ± SD	755.51 ± 512.63	
Median(25th-75th percentile)	685(392-877)	
Range	292-2518	
Ionized Calcium(mmol/L)		
Normal{1.12-1.32}	63	74.12%
Deranged	22	25.88%
Mean ± SD	1.16 ± 0.11	
Median(25th-75th percentile)	1.15(1.11-1.24)	
Range	0.82-1.31	

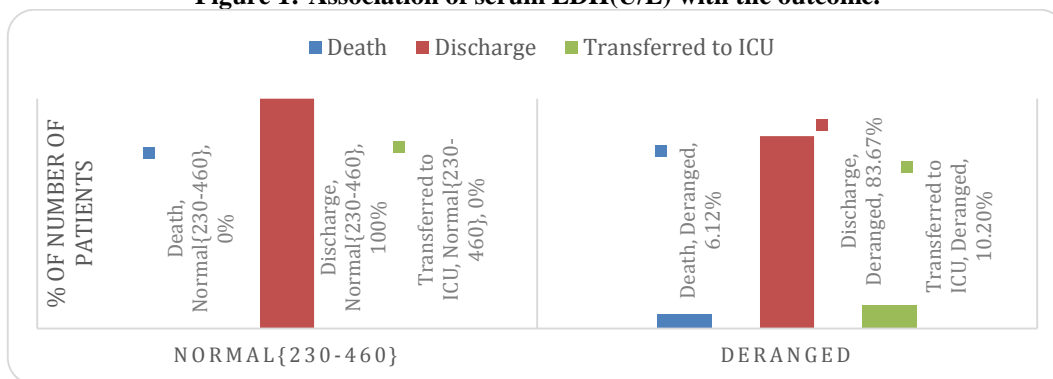
Table 2:-Association of serum LDH (U/L) with clinical diagnosis.

Serum LDH(U/L)	Dengue without a warning sign	Dengue with warning signs	Severe dengue	Total	P value
Serum LDH(U/L)					
Normal{230-460}	36 (100%)	0 (0%)	0 (0%)	36 (100%)	<.0001 [†]
Deranged	3 (6.12%)	32 (65.31%)	14 (28.57%)	49 (100%)	
Mean ± SD	380.38 ± 55.17	795.47 ± 98.84	1709.14 ± 510.28	755.51 ± 512.63	<.0001 [‡]
Median(25th-75th percentile)	388(339.5-412.5)	799.5(761-855.25)	1675.5(1272.25-2053.5)	685(392-877)	
Range	292-534	540-974	988-2518	292-2518	
* Fisher's exact test, [†] Chi square test, [‡] Kruskal Wallis test					

Table 3:-Association of ionized Calcium(mmol/L) with clinical diagnosis.

Ionized Calcium(mmol/L)	Dengue without warning sign(n=39)	Dengue with warning signs(n=32)	Severe dengue(n=14)	Total	P value
Normal{1.12-1.32}	39 (61.90%)	24 (38.10%)	0 (0%)	63 (100%)	<.0001 [*]
Deranged	0 (0%)	8 (36.36%)	14 (63.64%)	22 (100%)	
Mean ± SD	1.25 ± 0.03	1.13 ± 0.02	0.96 ± 0.06	1.16 ± 0.11	<.0001 [‡]
Median(25th-75th percentile)	1.26(1.235-1.27)	1.12(1.118-1.14)	0.99(0.965-1)	1.15(1.11-1.24)	
Range	1.2-1.31	1.08-1.16	0.82-1.01	0.82-1.31	
* Fisher's exact test, [‡] Kruskal Wallis test					

Figure 1:-Association of serum LDH(U/L) with the outcome.



Proportion of died patients was significantly higher in deranged serum LDH(U/L) (6.12%) as compared to normal serum LDH(U/L) {230-460}(0%). The proportion of patients who were transferred to ICU was significantly higher in deranged serum LDH(U/L) (10.20%) as compared to normal{230-460}(0%) (p value=0.031)The median (25th-75th percentile) of serum LDH(U/L) in patients who died was 2450 (2277-2484) which was significantly higher as compared to those transferred to ICU(1843 (1433-1902)) and discharged (534 (388-826)). (p value<0.0001).

Table 4:-Association of ionized Calcium(mmol/L) with the outcome.

Ionised Calcium(mmol/L)	Death (n=3)	Uneventful Discharge (n=77)	Discharged after ICU care (n=5)	Total	P value
Normal{ 1.12-1.32}	0 (0%)	62 (98.41%)	1 (1.59%)	63 (100%)	0.0002*
Deranged	3 (13.64%)	15 (68.18%)	4 (18.18%)	22 (100%)	
Mean ± SD	0.86 ± 0.05	1.18 ± 0.09	1.01 ± 0.06	1.16 ± 0.11	<.0001‡
Median(25th-75th percentile)	0.84(0.83-0.88)	1.2(1.12-1.26)	0.99(0.98-1)	1.15(1.11-1.24)	
Range	0.82-0.92	0.98-1.31	0.96-1.12	0.82-1.31	

* Fisher's exact test, ‡ Kruskal Wallis test

V. DISCUSSION:

This was a prospective observational study of 85 patients having dengue fever, meeting inclusion criteria, and admitted to medicine wards and ICU, SSG hospital, Vadodara to see for a correlation between serum calcium and LDH levels with the severity of dengue fever. The patients have grouped into three categories in our study and 45.88% of them had dengue without warning signs, 37.65% had dengue with warning signs and 16.47% had severe dengue. The maximum number of participants was in the age group of 18-27 years with 69.41% males and 30.59% females. In this study, the prevalence was higher in males than in females.

The distribution of symptoms in the study population showed that 100% of patients had fever followed by myalgia (77.65%), vomiting (60%), and headache (45.88%). Abdominal pain was seen in 22.35% of patients while arthralgia was seen in 29.41% of patients. Symptoms like retro-orbital pain and rash were observed in only 16.47% and 10.59% respectively while bleeding was seen in 10.59% and altered sensorium in 3.53% of patients with dengue fever. In another study done by Fu-Chun-Zhang et al., in Guangzhou province, China on 1032 subjects it was found that fever was seen in 100%, headache (90.9%), myalgia (68.4%), and skin rash in 60.1%. [3] It was further noted in this study that the mean value of systolic blood pressure among dengue fever patients was 105.51+/-13.11 with a median of 108, and the mean value of diastolic blood pressure was 69.48+/-7.36 with a median value of 70. Systolic blood pressure of <90mmhg was recorded in 7 out of 85 patients, who were found to have dengue fever with warning signs / severe dengue. Furthermore, the Hess test (tourniquet test) was done in all patients and was positive in 47.06% of patients and negative in 52.94%. The proportion of patients having dengue fever with warning signs and severe dengue was significantly higher with positive Hess test (57.50% and 30% respectively) as compared to a negative Hess test (20%, 4.44% respectively) with p-value < 0.0001. Radiological investigations like USG were suggestive of thickened and oedematous gallbladder wall in 85.88% of patients followed by ascites in 35.29% and hepato-splenomegaly in 27.06%. Our study focuses on the role of LDH and serum-ionized calcium as prognostic markers for determining the severity of dengue fever and its outcome in patients with dengue fever. In this study in the majority of patients, serum LDH was deranged (57.65%). The proportion of patients having dengue with warning signs and severe dengue was significantly

higher in deranged serum LDH as compared to normal (p-value <0.0001). Also, the median value of LDH was highest in patients with severe dengue (1675.5) followed by dengue with warning signs (799.5) followed by normal serum LDH in dengue without warning signs (388). In our study, the median value of LDH in patients who died was 2450U/L, which was significantly higher than those who were discharged after ICU care (1843U/L) and those who had uneventful discharge (534U/L). (p-value <0.0001). In a study done by Sirikutt P, Kalayanarooj on S. Serum lactate and lactate dehydrogenase as parameters for the prediction of dengue severity, it was found that values of serum LDH if increased to 1000 units on day 0 was a predictor for severe dengue or DHF / DSS with plasma leakage[4]. The levels of serum ionized calcium were also studied and the median value in dengue without warning signs was 1.26mmol/L, which was significantly higher compared to dengue with warning signs – 1.12mmol/L and severe dengue – 0.99mmol/L (p-value <0.0001). Hence it was seen that hypocalcemia is seen in severe dengue fever. The median of serum ionized calcium in patients who died was significantly lower 0.84mmol/L than in those who recovered after ICU stay (0.99mmol/L) and those who had an uneventful discharge (1.2mmol/L) (p-value <0.0001). These results are in line with another study done by V S Sheshan et al. named Analysis of Hypocalcaemia in Dengue and Correlation of Serum Calcium Levels with Severity of Dengue Disease wherein it was seen that out of 3 patients with severe hypocalcemia, 2 developed dengue shock syndrome and 1 developed dengue with warning signs [5]. Hence both LDH and Serum ionized calcium are emerging prognostic markers for determining the severity of dengue fever. Other parameters like platelet count, liver enzymes, and coagulation profile were also studied in patients with dengue fever. In our study, it was found that the median value of the platelet count of study subjects was 46000/mm³. The majority of the patients (80%) having dengue without warning signs had platelet count between 1.5-4.5lac/mm³ on admission while only 6.67% of patients with severe dengue had normal platelet count on admission (p-value < 0.055). Furthermore, the liver enzymes were also done and it was seen that in severe dengue SGPT was >300U/L in 92.86% of patients compared to 0% in patients of dengue without warning signs and 7.14% in patients of dengue with warning signs (p-value < 0.0001). Similarly, SGOT was >300U/L in 86.67% of patients with severe dengue as compared to dengue with warning signs (13.33%) and dengue without warning signs (0%) (p-value < 0.0001). Moreover, on assessing the coagulation profile it was seen that Prothrombin time (PT) was within normal limits in 92.77% of patients who were discharged, 6.02% of patients who were discharged after ICU care, and 1.20% of patients who died (p-value = 0.0008). Also, APTT (activated partial thromboplastin time) was normal in 94.67% of patients who had uneventful discharge, 4.00% of patients who were discharged after ICU stay, and only 1.33% of patients who died; hence indicating that patients who died had deranged PT/APTT on admission (p-value = 0.006). On other investigations like ECG, it was found that patients with severe dengue more commonly present with sinus tachycardia, and on USG findings like thickened and oedematous gall bladder, hepatomegaly, and ascites were seen more commonly in dengue with warning signs and severe dengue rather than dengue without warning signs. Thus towards the end of the study, we found that along with Serum LDH and serum ionized calcium other investigations like platelet count, liver enzymes, coagulation profile, and radiological investigations also give us a clue towards the severity and possible outcome of a patient with dengue fever. Since LDH and ionized calcium have a definitive role in prognosis they should be judiciously used.

VI. CONCLUSIONS:

- 1) Values of serum LDH are higher on admission in patients who died when compared with those who were discharged after ICU care or in those patients who were uneventfully discharged.
- 2) There is marked hypocalcemia seen in patients with severe dengue and it is also associated with death as an outcome, whereas in patients with dengue without warning signs and those discharged the values of serum calcium are in the normal range.
- 3) Thus, serum ionized calcium and serum LDH are useful biomarkers for predicting the severity and outcome of dengue fever patients.

LIMITATIONS:

- 1) We have a limited sample size; to apply inference to the community larger sample size is needed.
- 2) This was an observational study wherein serum calcium levels and LDH levels were done within 24hrs of admission; hence there was no uniformity on the day of investigating serum calcium and LDH. Their levels may have varied depending on the day of illness.
- 3) The other factors affecting calcium metabolism like phosphorous, magnesium, and PTH were not studied due to financial constraints.

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